American Red Cross
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National Headquarters
Washington, DC 20006

August 23, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Draft Guidance for Industry: Current Good Manufacturing Practice for Blood and Blood Components; (1) Quarantine aud Disposition of Prior Collections from Donors with Repeatedly Reactive Screening Tests for Hepatitis C Virus (HCV); (2) Supplemental Testing, and the Notification of Consignees and Transfusion Recipients of Donor Test Results for Antibody to HCV (Anti-HCV) [64 Fed. Reg. 33309 (1999) (Docket No. 98D-1878) June 22, 1999]

Dear Docket Officer:

This letter is to provide public comments on behalf of the American Red Cross (Red Cross) concerning the Food and Drug Administration's (FDA or Agency) Draft Guidance for Industry published on June 22, 1999 (the Guidance). The Guidance provides recommendations for blood collection facilities and their consignees for following Lookback procedures for donors who test positive for the Hepatitis C virus (HCV).

Red Cross, through its 37 Blood Services regions, supplies almost half of the nation's blood component transfusion needs. Red Cross has initiated efforts to comply with the previous HCV Guidances published on March 20, 1998, and September 23, 1998. The June 22 Draft Guidance, that is intended to eventually replace the current Guidance dated September 23, 1998, contemplates a number of changes that have a potentially far-reaching impact on blood facilities and their hospital customers. Therefore, we appreciate the opportunity to share additional. views With FDA relevant to the Agency's policies.

As a member. of the American Association of Blood Banks Interorganizational Task Force on HCV (the Committee), Red Cross first wishes to note that We fully agree with the comments submitted by the Committee-on this guidance, However, given the direct and very large impact of the contemplated. revisions, Red Cross wishes to express our views individually, as well.

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FDA's Guidance was intended to clarify the Agency's expectations with regard to autologous donors, retesting of donors, and to add new policies to include HCV 1 .O positive donors. The Guidance contains a mechanism for identifying donors with anti-HCV 1 .O EIA repeat reactive test results who may represent a risk of infection for transfusion recipients. We believe this mechanism, known as the "signal to cutoff ratio," is a reasonable process for determining which donors to include in 1 .O HCV Lookback.

However, the Guidance also, unexpectedly, extended the record-review portion of Lookback beyond the original timeframe for review of donations from donors who subsequently tested positive from 10 years to an indefinite period, In effect, this policy would require both the reopening and extension of 2.0/3.0 Lookback under the Agency's earlier guidances as well as the initiation of 1 .O Lookback for a large number of donors extending back indefinitely.

Red Cross' concerns are discussed below, chief of which is that the public health benefits of expanding Lookback in this manner are, at best; doubtful. Additionally, there is substantial room for open-ended interpretation of the guidance's expectations for "readily retrievable" records. Given the differences in storage media and other conditions, there is little support for the Agency's expectation that extension will produce records that are useable as well as retrievable. Finally, the -extension may actually do more harm than good. Recipients of blood products, such as hemophiliacs and transfusion recipients may be led to believe that, if no notification during this targeted Lookback is received, they are not at risk, when, in actuality, they may not receive such a notification due to either lack of manufacturing records, lack of transfusion service records, or lack of ability to trace recipients.

Indefinite Lookback

By setting up a requirement for an "indefinite" Lookback, the draft Guidance has defined a set of requirements that is far more sweeping that originally envisioned. Specifically:

Section III. 1 .A., Quarantine of Prior Collections from Donors Who Subsequently Test Repeatedly Reactive for anti-HCV, states:

> "Blood establishments should identify prior collections extending back *indefinitely* to the extent that electronic or other readily retrievable records exist." [emphasis added]

Section III.2.A., Review of Records and Quarantine of Prior Collections, states:

> "The record search should extend back *indefinitely* to the extent that electronic or other readily retrievable records exist." [emphasis added], and,

Section III.2.B., Notification of Consignees and Transfusion Recipients, states:

> "For previously distributed blood or blood components collected from the same donor dating back *indefinitely* (that is, prior-to January 1, 1988), blood establishments should begin notification of consignees as soon as feasible. This notification of consignees should be completed by September 30, 2000," [emphasis added] and

Section III.3.A., Review of Records and Quarantine of Prior Collections, states:

> "The record search should. extend back *indefinitely* to the extent that electronic or other readily retrievable records exist.'.'. [emphasis added]

The Canadian Red Cross and its successors have been performing in&finite Lookback for their positive HCV donors for approximately five years. They have found a diminishing rate of return in their ability to find and contact recipients that directly correlates with the length of time for which the donation dates extend back, It has been estimated that the current Lookback, which extends back to donations collected in 1988, will reach only 1% of patients that received blood before 1990. Clearly, the further back in time the Lookback is extended, the smaller the rate of return will become.

The "Model of Success Rate for HCV Lookback" (Attachment I) provides a prediction for the rate of success of contacting at-risk transfusion recipients who then present for testing and the success rate of contacting recipients who do not already know that they are anti-HCV positive. The model uses data from a survey of Red Cross' 37 regions and their consignees, but it does not correct for either the retrievability or the usefulness of the records. The consignee response rate to the survey was 62% (2076/3370). The model shows that the likelihood of a HCV positive donor being traced to a recipient who then presents for testing (contact success rate) is only 2% ten years after the transfusion. It also shows that the likelihood of tracing a HCV positive donor to a recipient who learns for the first time of their HCV infection (medical success rate) is 1% ten years after the transfusion.[1]

There are no hard and fast numbers established for success rates to be used when setting Lookback timeframes. However, once the interval between a donation and the Lookback initiative is greater than 8-10 years, the exercise is highly unlikely to achieve the medical-objective. Investigations should be limited to donations within the 10 years

[1] See Attachment II for a review of the consignee responses received by one Red Cross region.

prior to the time of the investigation, regardless of when the donors were originally found to be HCV positive.[2]

Red Cross strongly believes that the targeted Lookback should not be extended indefinitely, that it should go back an identified, limited time period. Thus, Red Cross recommends that: (1) for prospective Lookback, a rolling 10 years be the required time frame for all new Lookback cases, and (2) for retrospective Lookback, the indefinite requirement be deleted and that all Lookback go back no further than January 1, 1988.

Records

Red Cross thinks it still must comment on the term "readily retrievable" as there are many possible definitions. This term will give rise to a wide variation of interpretation not only among the various blood collectors but also between these establishments and the FDA.. Further, without clear and consistent parameters on how to define "readily retrievable," FDA investigators may interpret the guidance differently among themselves. This potential disparity permits no clear prediction or expectations-for blood establishments undergoing inspections.

Along with the diminishing rate of return as the length of the Lookback is extended, there is a concurrent incremental decrease in the uniformity and condition of the records resulting in a diminishing value to the review, even' if the records exist. For example, as collection facilities deal with older storage media, the logistics, training and quality control assessments associated with the review of those records become more significant. Thus, older-records for each donation require more blood bank staff time to research the donation, component, and shipping records.

Moreover, when dealing with older records, there is little assurance of a direct link, such as direct coding, between the component production record and other records that trace components to the final shipping location so that the consignee and, eventually, the recipient can be identified. For example, while older order and distribution records may be on microfilm or microfiche, they are ordered by date of issue. To determine if a component was shipped for transfusion, a search of the records during the entire dating period of the component will be required (i.e., up to 45 days for a Red Blood Cell or 12 months for a Fresh Frozen Plasma).

Red Cross believes that only records that can be located and linked together within 10 working days from the beginning of the search should be considered "readily retrievable." But this interpretation may not be universally acceptable to either other blood establishments or to FDA investigators.

[2] The implication from the model is that Lookback for HCV 1 .O on a donation in 1990, investigated in 1999, should encompass 1989 and 1990 donations only.

The term "readily retrievable" also does not address whether the records themselves are reasonably legible. Over time, microfiche can fade, ink becomes smeared, and handwriting that is not clear to begin With can become unreadable from exposure to heat, or other normal environmental conditions. Thus, older documents may be "retrievable" but may not be usable.

HCV 1.0 Signal to Cut Off Calculation

Section III.3.B.2.(i) states that signal to cut off (S/CO) calculations should be done on three anti-HCV EIA test results and that the Lookback decision be made based on whether two of the three.calculations-are less than or equal to/greater than 2.5.

-- This section should also permit S/CO calculations even when only two EIA test results are available. If the S/CO values agree, a Lookback decision can be made, but if one value is <2.5 and the, other value is ≥ 2.5, then either further testing using a stored or new sample should be performed prior to making a Lookback decision or Lookback should be required:

Completion Period

Red Cross is further concerned by the requirement'that all of the additional retrospective Lookback notifications must be completed by September 30, 2000. The proposed new requirements to include both EIA 1 .O positive donors as well as the indefinite extension of the record review for 2.0/3.0 positive donors cannot be completed within six months after the March 23, 2000, deadline for the current Lookback requirements. This expectation is even more unrealistic given the greater difficulty of reviewing significantly older records as described previously. Red Cross supports the Committee's recommendation that with or without an indefinite Lookback, the Lookback for 1 .O positive donors should begin by May 1, 2000, and the Lookback be completed by May 1, 2001.

Public Health Campaign

Red Cross strongly believes that a public health education effort aimed at specific high risk groups in combination with the current targeted Lookback requirements (including the EIA 1 .0 Lookback requirements) is a much more effective mechanism to reach those at-risk of HCV infection. A targeted Lookback may actually be detrimental to the overall public health, because recipients may be falsely convinced that, if they are at-risk, they will receive' a notification. In reality, they may not. Given the diminishing rate of return from notifications and the constraints on record review, there can be no assurance that a targeted Lookback will reach all at-risk transfusion recipients, Moreover, those at far greater risk, such as IV drug users, will receive no notification.

'The public health notifications for physicians and health care providers already initiated by the Centers for Disease Control are a good start. Additional public notifications and similar communications will have an equal or greater chance of reaching those at risk of contracting HCV than the extended Lookback will have.

A complete public education program should reach most of the remaining recipients who received transfusions before the current January 1, 1988 cutoff. Such education programs could target audiences most likely to have received a transfusion; such as hemophiliacs and women who have delivered through Caesarian sections. It would also better meet the real public need of identification and treatment of HCV positive persons by providing the basic information to a much larger group of at risk individuals.

In- sum, Red Cross urges FDA to revise the Lookback to retain the 10 year Lookback timeframe. This requirement-is extensive and is consistent with. all available evidence that those recipients most at risk are most likely to receive-a notification. Additional notifications should-be carried out through alternative public health education mechanisms and other means.' Longer term, alternative mechanisms for notification are more likely to reach those at risk of HCV exposure than an indefinite Lookback can realistically accomplish.

Again, Red Cross appreciates the opportunity to submit its views on the Guidance to the FDA. If there are any questions on this letter, or if you wish to meet to discuss these concerns in greater detail, please contact Anita Ducca, Director, Regulatory Relations, at 703-3 12-560 1.

Sincerely,

Anita T. Ducca for

Glenn M. Mattei, Esq.
Senior Director, Quality Assurance and
Regulatory Affairs
Biomedical Services
American Red Cross

Attachments

cc: Paul Mied, Ph.D.

MODEL OF SUCCESS RATE FOR HCV **LOOKBACK**
Estimates from published studies and 3/99 Red Cross survey

Years

current retrospective lookback possible intervals
current prospective lookback possible intervals
proposed lookback possible intervals

# years between donation/transfusion and lookback investigation (1)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
% donor programs with records linking donor to donations (2,3)	100	100	100	100	100	100	100	100	loo	100	97	94	91	88	85	82	78	75	72	68
% donor programs with records liking donation to components (2,3)	100	100	100	100	100	100	100	100	100	100	95	90	85	80	75	70	65	60	55	51
% donor programs with records linking component to consignee (2,3)	100	100	100	100	100	100	100	loo	100	9 5	90	85	80	75	70	65	60	55	50	46
% transfusion programs with records linking component to final disposition (3,4)	99.6	99.4	99.1	98.4	97.8	91.9	88.1	83.7	80	75	67.1	51.1	46.5	42	36.6	31.5	28.6	25.4	22.7	18.1
% components transfused (5)	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
% living recipients (6)	50	44	38	32	26	20	17	12	10	9	8	7	6	5	5	5	5	5	5	5
% recipient hospital records with valid addresses(7)	100	92	84	76	70	60	50	50	40	40	40	30	30	30	25	25	25	20	20	20
% recipients contacted who present for testing(8)	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75
♦ contact success Rate (9)	32%	26%	20%	15%	11%	7%	5%	3%	2%	2%	1%	1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%
% test positive, recipients who didn't already know (10)	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45
♦ Medical Success Rate (11)	14%	12%	9%	7%	5%	3%	2%	1%	1%	1%	1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%

(1) lookback year to donation year, ie for index donations in 1991 subjected to retrospective lookback in 1999, the interval begins at 8 years and goes up from there
(2) extrapolated from ARC 3/99 survey
(3) frequency of records available; no correction for whether they are organized, in one location, physically accessible, successfully located, etc.
(4) directly from ARC 3/99 survey; no correction for whether they are organized, in one location, physically accessible, successfully located, etc.
(5) Canadian experience reported in Transfusion 1999; 39: 194-200; East coast ARC region experience with 200 responses on 397 notifications had 23/200 components not transfused is 88%
(6) findings from CJD Lookback Study, confirmed by Canadian experience
(7) extrapolation from Canadian experience report, which had 30% lost to followup at a median of 5 years transfusion-to-lookback interval
(6) Canadian experience reported 100% response: Pittsburgh experience per Dr. Triulzi is that about half respond. Used an intermediate number.
(9) likelihood of being able to trace from HCV positive donor to a living recipient who gets tested
(10) Canadian experience was 61% positive of which 53% already knew. Assume US patients half as likely to have already been tested (assume 26% already know)
(11) likelihood of tracing from an HCV positive donor to a recipient who teams for the first time that he/she is infected with HCV.

REVIEW OF CONSIGNEE RESPONSES TO HCV LOOKBACK FROM ONE RED CROSS REGION

This east coast region collects about 160,000 donations per year. To date, the region has sent 397 Lookback notifications and has received 200 responses. A review of the consignee responses is provided below. The recipient contact success rate for this region is better than the model in Attachment I: 4.5% vs. 1 %. However, even with a better contact rate, the medical success rate is worse than the model: 0% vs. 1%.

	# of Responses	Years post transfusion
Deceased recipients	132 (65%)	N/A
Recipients lost to follow up	5 (3%)	7, 9, 10
Discarded components	23 (12%)	N/A
Transfusion service reported recipient not notified or unknown	29 (15%)	N/A
Newly tested recipients (nonreactive)	9 (5%)	6, 8, 9, 10, 11
Recipients (positive, previously known)	2 (1%)	*
Total Responses Received	200	N/A

* One of these donors was tested for HCV in 1998, and the other was tested twice, once in 1991 and a second time in 1994.

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